09/857054

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER 49589

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP 99/09309	**30 November 1999**	**1 December 1998**

TITLE OF INVENTION: METHOD FOR PRODUCING SOLID FORMS OF ADMINISTRATION BY MELT EXTRUSION

APPLICANT(S) FOR DO/EO/US Gunther BERNDL, Stephan KOTHRADE, Thomas KESSLER, Armin LANGE, Juergen HOFMANN, Ulrich REINHOLD

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. /X/ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.

2. / / This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.

3. /X/ This express request to begin national examination procedures (35 U.S.C.371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. /x/ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. /X/ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).

   a./X/ is transmitted herewith (required only if not transmitted by the International Bureau).
   b./ / has been transmitted by the International Bureau.
   c./ / is not required, as the application was filed in the United States Receiving Office (RO/US0).

6. /X/ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. / / Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).

   a./ / are transmitted herewith (required only if not transmitted by the International Bureau).
   b./ / have been transmitted by the International Bureau.
   c./ / have not been made; however, the time limit for making such amendments has NOT expired.
   d./ / have not been made and will not be made.

8. / / A translation of the amendments to the claims under PCT Article 19(35 U.S.C. 371(c)(3)).

9. /X / An oath or declaration of the inventor(s)(35 U.S.C. 171(c)(4)).

10./ / A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11./ / An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12./X / An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13./X / A FIRST preliminary amendment.
/ / A SECOND or SUBSEQUENT preliminary amendment.

14./ / A substitute specification.

15./ / A change of power of attorney and/or address letter.

16./x / Other items or information.
International Search Report
International Preliminary Examination Report

U.S. Appln. No. (If Known)	INTERNATIONAL APPLN. NO. PCT/EP99/09309	ATTORNEY'S DOCKET NO. 49589

17. /X/ The following fees are submitted	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO.....$860.00	**860.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$750.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$700.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO .....$ 970.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied pro -visions of PCT Article 33(2)-(4).....$96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than / / 20 / /30 months from the earliest claimed priority date (37 CFR 1.492(e)).		

Claims	Number Filed	Number Extra	Rate		
Total Claims	**6**	-20	X$18.		
Indep.Claims	2	-3	X$80.		
Multiple dependent claim(s)(if applicable)		+270.			
TOTAL OF ABOVE CALCULATION			=	860.00	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).					
SUBTOTAL			=	860.00	
Processing fee of $130. for furnishing the English translation later than / /20 / /30 months from the earliest claimed priority date (37 CFR 1.492(f)).		+			
TOTAL NATIONAL FEE			=	**860.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) $40.00 per property		=		40.00	
TOTAL FEES ENCLOSED			= $	**900.00**	
			Amount to be refunded:	$	
			Charged	$	

a./X/ A check in the amount of $ 900. to cover the above fees is enclosed.

b./ / Please charge my Deposit Account No._____in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c./X/ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **11-0345**. A duplicate copy of this sheetis enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.

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Herbert B Keil
SIGNATURE

Herbert B. Keil
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of)
BERNDL et al.) BOX PCT
)
International Application)
PCT/EP 99/09309)
)
Filed: November 30, 1999)
)

For: METHOD FOR PRODUCING SOLID FORMS OF ADMINISTRATION BY MELT MIX

PRELIMINARY AMENDMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Prior to examination, kindly amend the above-identified application as follows:

IN THE CLAIMS

Please amend the claims as shown in the attached sheet.

REMARKS

The claims have been amended to eliminate multiple dependency and to put them in better form for U.S. filing. No new matter is included. A clean copy of the claims is attached.

Favorable action is solicited.

Respectfully submitted,

KEIL & WEINKAUF

/HBKeil

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(202)659-0100

AMENDMENTS TO THE CLAIMS - OZ 0050/49589 - Preliminary Amendment

4. The method in accordance with claim 1 [one of claims 1 to 3], characterized in that a planetary roller extruder (10) without kneading disks is used.

5. The method in accordance with claim 2 [one of claims 2 to 4], characterized in that the number of revolutions of the central spindle (14) of the planetary roller extruder (10) is set in such a way that the dwell time in the extruder (10) of a pharmaceutical mixture to be extruded is approximately 0.5 to 2 minutes.

CURRENT CLAIMS - OZ 0050/49589

1. A method for producing solid forms of administration by melt extrusion, wherein a polymeric binder, at least one active pharmaceutical agent and, if required, further additives are mixed in an extruder and melted, and are subsequently extruded in a continuous ductile production string, characterized in that a planetary roller extruder (10) is used as the extruder.

2. The method in accordance with claim 1, characterized in that a planetary roller extruder (10) with a central spindle (13) and three to eight planetary spindles (14) are used.

3. The method in accordance with claim 2, characterized in that a planetary roller extruder (10) with six planetary spindles (14) is used.

4. The method in accordance with claim 1, characterized in that a planetary roller extruder (10) without kneading disks is used.

5. The method in accordance with claim 2, characterized in that the number of revolutions of the central spindle (14) of the planetary roller extruder (10) is set in such a way that the dwell time in the extruder (10) of a pharmaceutical mixture to be extruded is approximately 0.5 to 2 minutes.

6. Use of a planetary roller extruder for extruding a heat- and/or shear-sensitive pharmaceutical mixture.

Method for Producing Solid Forms of Administration by Melt Extrusion

The present invention relates to a method for producing solid forms of administration by melt extrusion.

In contrast to conventional tableting methods, which are based on compacting powders or granules, in melt extrusion a melt of a polymer of thermoplastic material, which is water-soluble or capable of swelling in water and contains active ingredients, is processed. Methods for producing tablets and other forms of administration by means of melt extrusion are known, for example, from EP-A 0 240 904, EP-A 0 240 906, EP-A 0 337 256, US-A 4,880,585 and EP-A 0 358 105.

There, an extrudable pharmaceutical mixture is created by mixing and melting a polymeric binder agent, at least one active pharmaceutical ingredient and possibly further additives. An extruder is customarily employed for mixing and melting. However, the individual components can also be mixed prior to their introduction into the extruder. The melt containing active ingredients is pressed out through one or several extrusion dies, for example slot dies in the extruder head, in the form of product strings or tapes. Then the still ductile product strings or tapes are shaped into tablets or other forms of administration, such as suppositories or granules, with the aid of suitable tools. For example, the extruded melt can be compressed into shapes complementary to the desired form of administration by means of a calendering method with counter-rotating shaping rollers. To this end, depressions complementary to the shape of the desired tablet or suppository are provided in one or both shaping rollers. In accordance with another known variation, a tape, which has

depressions or openings in the desired tablet or suppository shape, is passed between smooth calendering rollers.

Single- or twin-screw extruders are customarily employed as extruders. A method for producing solid pharmaceutical dispersions is described in European Patent EP-B 0 580 860, in which a twin-screw extruder having kneading disks is employed. The employment of multi-screw extruders in the course of the production of pharmaceutical compositions is mentioned in European Patent Application EP-A 0 729 748. But actually this document only deals with twin-screw extruders with kneading disks. Extruders with more than two screws are not described either in EP-B 0 580 860 or in EP-A 0 729 748.

However, such twin-screw extruders have the disadvantage that spot-like occurring temperature peaks and large shear stresses act on the material to be plasticized in the area of the kneading disks. This poses a problem, particularly for the extrusion of melts containing active ingredients, since many active ingredients are extremely sensitive to heat. Moreover, only those polymeric binders and additives which are insensitive to increased temperatures and high shear stresses can be used in conventional twin-screw extruders with kneading disks. These disadvantages greatly limit the range of substances which are customarily employed in tablet making by means of melt extrusion.

It is therefore the object of the present invention to provide a method for producing solid forms of administration by means of melt extrusion, which makes it possible to plasticize the original substances of the extrudable mixture, i.e. the polymeric binders and the active pharmaceutical compositions in particular, in a gentle manner, in particular without the appearance of high shear and temperature stresses, and to mix them.

This object is attained by the method in accordance with the attached main claim. In accordance with the invention, for the production of solid forms of administration by means of melt extrusion it is proposed to mix a polymeric binder, at least one active pharmaceutical composition, and possibly further additives in a planetary roller extruder, to melt them and to subsequently extrude them in the shape of a continuous ductile production string.

Surprisingly it was found that, when employing a planetary roller extruder, it is possible to also work sensitive polymers, materials and additives into a solid form of administration.

Planetary roller extruders are known per se and for example are produced in Germany by Entex Rust & Mitschke GmbH of Bochum.

Planetary roller extruders are continuous screw kneaders, whose kneading element is embodied in the manner of a planetary rolling mill. The same as conventional single- and twin-screw extruders, planetary roller extruders also have a material inlet, which is followed by a plastification and homogenization zone. A cooling zone for cooling the heated material mixture to the extrusion temperature is customarily arranged upstream of the outlet nozzle. The plastification and homogenization zone has a central spindle, which typically is notched at less than 45o. Several planetary spindles mesh with this central spindle and, in turn, engage a cylindrical bushing with teeth on the interior. When the central spindle is driven, the planetary spindles freely rotate in a rolling-off process between the bushing and the central spindle. They are not seated and swim in the material to be extruded during the operation. To the extent that the teeth are in engagement with the central spindle, or the interior teeth of the bushing, each planetary spindle represents a sort of a

propeller pump. The material to be plasticized is typically pushed axially into the plastification and homogenization zone of the planetary roller extruder and is very extensively rolled out between the rotating planetary spindles and the central spindle, on the one hand, or the bushing with interior teeth on the other hand.

The material to be plasticized which reaches the gap clearance between the teeth is repeatedly subjected to a short term spot-shaped rolling stress but, because of the roll-off movement of the planetary spindles on the central spindle, is immediately relaxed again and released. The material absorbs the required plastification heat in a very short time because of this thin film rolling and is intensely mixed and kneaded and homogenized in the process.

Planetary roller extruders are customarily of very short construction because of their considerably higher efficiency in respect to single- and twin-screw extruders, so that the dwell times of the material to be extruded in the plastification and homogenization zone are also very short.

If required, the plasticized and homogenized material is grasped by a downstream-connected short discharge screw and can be extruded through breaker plates or other nozzles. However, the extruder can also be operated without die plates and without a pressure buildup.

The plastification and homogenization zone of the extruder is customarily heatable. To this end, heating or cooling means, for example, can be conducted through the housing jacket of the extruder surrounding the bushing.

The planetary roller extruder is particularly advantageously constructed in a module-like manner from individual

sections, wherein the layout of the rollers and the temperature profile can be separately optimized for each section.

The planetary roller extruder is distinguished by easy self-cleaning properties, which is particularly advantageous when producing pharmaceuticals.

The pressureless chambers existing between the roller units assure sufficient degassing of the material to be plasticized.

In spite of the short-term temperature and shear stresses, it is possible by means of the method of the invention to achieve the optimum homogenization of the material in the shortest time. This has shown itself to be advantageous when producing solids solutions, since it becomes possible to achieve a molecularly dispersed distribution of the active ingredient in the matrix without the use of solvents and high temperatures.

On the average, with the method of the invention, i.e. the employment of a planetary roller extruder, the temperatures needed for plasticizing and homogenizing the pharmaceutical mixture are approximately 20°C lower than the temperatures required by the conventional extrusion methods, i.e. when using a twin-screw extruder.

A planetary roller extruder having a central spindle and three to eight planetary spindles is advantageously used.

The use of a planetary roller extruder having six planetary spindles is particularly preferred. It is possible by means of this arrangement to mix and plasticize the mixture to be extruded particularly effectively without excessive temperature and shear stresses of the material occurring.

The planetary roller extruder does not require kneading disks because of the good intermixing and plastification of the pharmaceutical mixture. The above described disadvantages

occurring, for example, when twin-screw extruders with kneading disks are employed, are avoided with the method in accordance with the invention.

The dwell time of the pharmaceutical mixture in the planetary roller extruder is short and preferably is approximately 0.5 to 2 minutes, depending on the number of revolutions of the central spindle and the length of the roller element.

Since in accordance with the method of the invention the material to be plasticized is not subjected to temperature and shear stresses lasting over a long time, a planetary roller extruder is particularly suitable for extruding materials which contain heat- or shear-sensitive substances, which can be active material, excipients or added materials here.

Therefore the use of a planetary roller extruder for extruding a heat-sensitive pharmaceutical mixture is also an object of the invention.

Within the scope of the present invention, the term "form of administration" should be understood in its broadest possible sense. It is tied neither to any definite shape nor to a definite application. It therefore includes, for example, tablets for peroral application, suppositories for rectal application, granules, or even larger shapes, such as cubes, blocks (cuboids) or cylindrical shapes. The method in accordance with the invention is suitable for producing any arbitrary forms of administration, which are finding use, for example, as medicaments, plant treatment agents, feeds and foodstuffs, as well as for the release of scents and essential oils.

All materials having a pharmaceutical effect and the least possible side effects are understood to be active pharmaceutical agents, provided that they do not decompose under the processing

conditions. The amounts of effective agent per unit of dosage and the concentration can vary within wide limits, depending on their effectiveness and speed of release. The only condition here is that they are sufficient for obtaining the desired effects. The concentration of active agents in respect to the total weight of the form of administration therefore can lie in the range between 0 and 90, preferably between 0.1 and 60. In the present connection, the term active ingredient also includes any arbitrary combinations of active ingredients. For example, vitamins are also active ingredients in the sense of the invention. Preferred active ingredients are ibuprofen (in the form of racemates, enantiomers or enriched enantiomers), ketoprofen, flurbiprofen, acetylsalicylic acid, verpamil, paracetamol, nifedipin and catopril.

But the method in accordance with the invention is particularly suitable for heat-sensitive substances such as, for example, enzymes, peptides, vitamins, hormones, insulin, plant extracts, dihydropyridine derivatives, antibiotics, for example makrolyte or zytostatic agents. The method in accordance with the invention is also particularly suited for the extrusion of plant extracts and other natural active ingredients.

The method in accordance with the invention is particularly suited for producing solid forms of administration containing those polymers which, because of their high molecular weight or thermolability, are subject to decomposition phenomena in the course of extrusion in twin-screw extruders, for example oxidative degradation, depolymerization, molecular weight loss, elimination of side groups, or which enter into chemical reactions with other components of the formulation.

In the total mixture of all components, the polymeric

binder must soften or melt in the range between 50 and 250°C, preferably 60 to 180°C, and particularly preferred in the range between 80 to 150°C. Therefore the glass transition temperature of the mixture must lie below 200°C, preferably below 150°C, and particularly preferred below 130°C. If required, it will be reduced by conventional, pharmacologically acceptable plasticizing excipients. Suitable polymeric binders are described in WO 97/15291, for example.

The following are preferably employed as polymeric binders for the melt extrusion of active pharmaceutical agents: polymers or copolymers of N-vinyl pyrrolidone, eudragit types (acrylic resins) or celluloses. Particularly preferred here are: polyvinyl pyrrolidone (PVP), copolymers of N-vinyl pyrrolidone and vinyl esters, such as vinyl acetate, poly(hydroxyalkylacrylates), poly(hydroxyalkylmethacrylates), polyacrylates, polymethacrylates, alkyl celluloses or hydroxyalkyl celluloses.

Besides the polymeric binder and the active ingredient(s), the extrudable mixture can also contain customary additives, for example plasticizers, lubricants, solvents, dyestuffs, stabilizers, or wetting, preservative, blasting, adsorption, unmolding and expanding agents. Also, customary galenic excipients, for example extenders or fillers, can be contained in it. Suitable additives and galenic excipients are described in WO 97/15291, for example.

The typical structure of a planetary roller extruder is shown in a sectional representation in the attached drawing.

Following its plastification and homogenization area, the planetary roller extruder 10 has a heatable, essentially cylindrical housing jacket 11, on whose interior wall a bushing 12 is arranged, out of whose interior surface a helical groove 12a

has been cut. A driveable central spindle 13 is rotatably seated centered in the interior of the bushing 12 and is surrounded by several freely rotating planetary spindles 14. Each planetary spindle 14 meshes with its helical outer surface 14a with the helical outer surface 13a of the central spindle 13, as well as with the interior spiral 12a of the bushing 12. The bushing 12 is arranged, fixed against relative rotation, in the housing of the planetary roller extruder 10. A thrust ring, not visible in the sectional representation of the attached drawing figure, for the rotating planetary spindles 14 is arranged at the extruder end.

Example 1:

Production of a Solids Solution of Ibuprofen in a Matrix of Kollidon 90 F, Using a Planetary Roller Extruder

30 wt.-% of ibuprofen were extruded together with 69.5 wt.-% of Kollidon 90 F of a k value of 90, and with 0.5 wt.-% of Aerosil 200 in a planetary roller extruder.

The planetary roller extruder had a central spindle of a diameter of 43 mm, which was surrounded by six planetary spindles each of a diameter of 20 mm and of a length of 398 mm each. Extrusion was performed at a number of revolutions of 40 rpm and with a throughput of 5kg/h.

Plasticizing and homogenizing took place at a maximum temperature in the extruder of 150°C.

Following extrusion, the k value of Kollidon was 85.

Comparison Example 1:

Production of a Solids Solution of Ibuprofen in a Matrix of Kollidon 90 F, Using a Twin-Screw Extruder

30 wt.-% of ibuprofen were extruded together with 69.5 wt.-% of Kollidon 90 F of a k value of 90, and with 0.5 wt.-% of Aerosil 200 in a ZSK twin-screw extruder of the Werner & Pfleiderer company at a number of revolutions of 100 rpm and a throughput of 2 kg/h.

A maximum temperature in the extruder of 190°C was required for satisfactory plasticizing and homogenizing.

Following extrusion, the k value of Kollidon was only approximately 70.

Claims

1. A method for producing solid forms of administration by melt extrusion, wherein a polymeric binder, at least one active pharmaceutical agent and, if required, further additives are mixed in an extruder and melted, and are subsequently extruded in a continuous ductile production string, characterized in that a planetary roller extruder (10) is used as the extruder.

2. The method in accordance with claim 1, characterized in that a planetary roller extruder (10) with a central spindle (13) and three to eight planetary spindles (14) are used.

3. The method in accordance with claim 2, characterized in that a planetary roller extruder (10) with six planetary spindles (14) is used.

4. The method in accordance with one of claims 1 to 3, characterized in that a planetary roller extruder (10) without kneading disks is used.

5. The method in accordance with one of claims 2 to 4, characterized in that the number of revolutions of the central spindle (14) of the planetary roller extruder (10) is set in such a way that the dwell time in the extruder (10) of a pharmaceutical mixture to be extruded is approximately 0.5 to 2 minutes.

6. Use of a planetary roller extruder for extruding a heat- and/or shear-sensitive pharmaceutical mixture.

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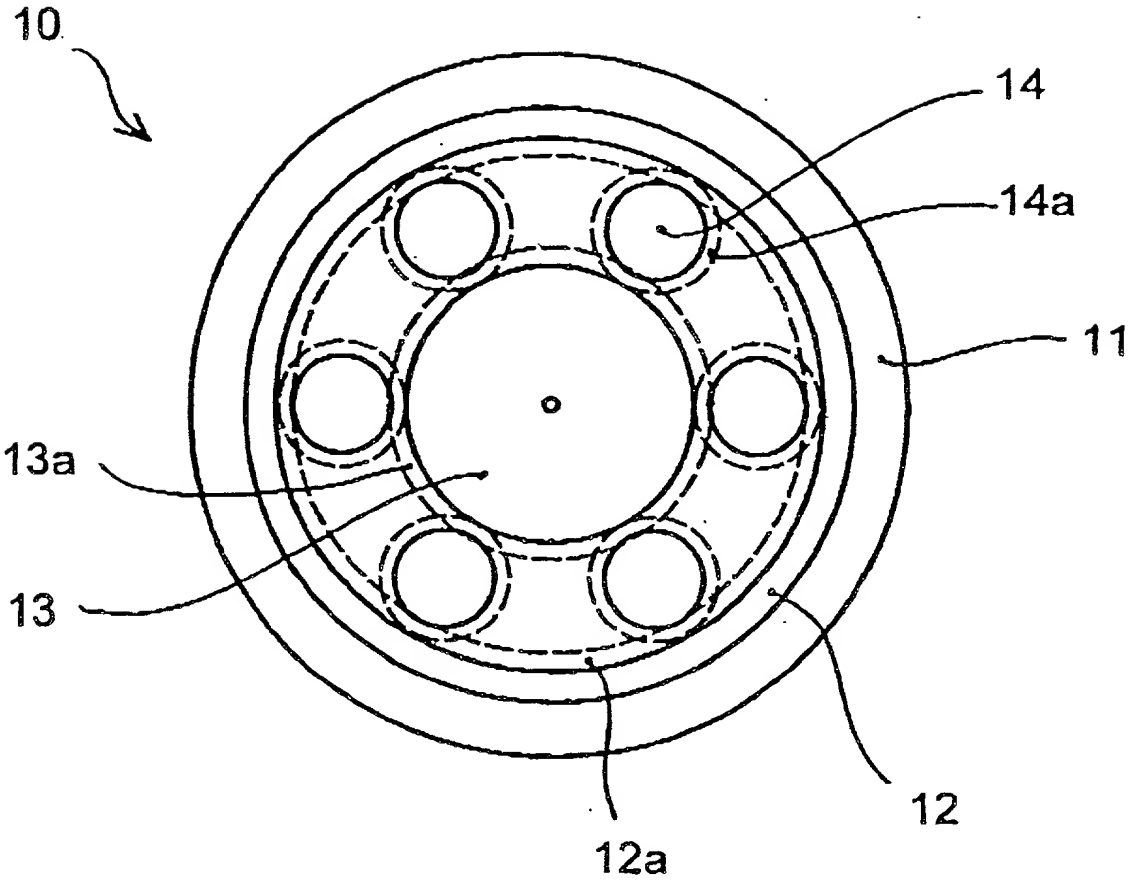

Fig.

Declaration, Power of Attorney

0050/049589

We (I), the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Method for producing solid forms of administration by melt extrusion

the specification of which

[X] is attached hereto.

[ ] was filed on _____ as

Application Serial No. _____

and amended on _____.

[x] was filed as PCT international application

Number PCT/EP99/09309

on November 30, 1999

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above–identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)–(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	**Country**	**Day/Month/Year**	**Priority Claimed**	
19855440.0	*Germany*	*01 December 1998*	[x] Yes	[ ] No

We (I) hereby claim the benefit under Title 35, United States Codes, § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	**Filing Date**	**Status (pending, patented, abandoned)**

And we (I) hereby appoint **Messrs. HERBERT. B. KEIL**, Registration Number 18,967; and **RUSSEL E. WEINKAUF**, Registration Number 18,495; the address of both being Messrs. Keil & Weinkauf, 1101 Connecticut Ave., N.W., Washington, D.C. 20036 (telephone 202–659–0100), our attorneys, with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to sign the drawings, to receive the patent, and to transact all business in the Patent Office connected therewith.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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